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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/560,509	08/29/2006	Duncan Hiscock	PZ0386	5657

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Amersham Health Inc
IP Department
101 Carnegie Center
Princeton, NJ 08540

EXAMINER	
SCHLIENTZ, LEAH H	

ART UNIT	PAPER NUMBER
1618	

MAIL DATE	DELIVERY MODE
08/25/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/560,509	HISCOCK ET AL.	
	Examiner	Art Unit	
	Leah Schlientz	1618	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 December 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1 and 3-31* is/are pending in the application.

4a) Of the above claim(s) *5-9,11,15 and 19-25* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3,4,10,12-14,16-18 and 26-31* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *12/13/2005*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

This application contains claims directed to the following patentably distinct species: caspase-3 inhibitor and imaging moiety. The species are independent or distinct because claims to the different species recite the mutually exclusive characteristics of such species. In addition, these species are not obvious variants of each other based on the current record.

Applicant is required under 35 U.S.C. 121 to elect a single disclosed species for prosecution on the merits to which the claims shall be restricted if no generic claim is finally held to be allowable. Currently, the claims are generic.

There is an examination and search burden for these patentably distinct species due to their mutually exclusive characteristics. The species require a different field of search (e.g., searching different classes/subclasses or electronic resources, or employing different search queries); and/or the prior art applicable to one species would not likely be applicable to another species; and/or the species are likely to raise different non-prior art issues under 35 U.S.C. 101 and/or 35 U.S.C. 112, first paragraph.

Applicant is advised that the reply to this requirement to be complete must include (i) an election of a species to be examined even though the requirement may be traversed (37 CFR 1.143) **and (ii) identification of the claims encompassing the elected species**, including any claims subsequently added. An argument that a

claim is allowable or that all claims are generic is considered nonresponsive unless accompanied by an election.

The election of the species may be made with or without traverse. To preserve a right to petition, the election must be made with traverse. If the reply does not distinctly and specifically point out supposed errors in the election of species requirement, the election shall be treated as an election without traverse. Traversal must be presented at the time of election in order to be considered timely. Failure to timely traverse the requirement will result in the loss of right to petition under 37 CFR 1.144. If claims are added after the election, applicant must indicate which of these claims are readable on the elected species.

Should applicant traverse on the ground that the species are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the species to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the species unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103(a) of the other species.

Upon the allowance of a generic claim, applicant will be entitled to consideration of claims to additional species which depend from or otherwise require all the limitations of an allowable generic claim as provided by 37 CFR 1.141.

During a telephone conversation with Craig Bohlken on 8/12/2009 a provisional election was made of compound 5A of Example 13. Affirmation of this election must be

made by applicant in replying to this Office action. The election reads on species 2-oxindole sulphonamide as caspase-3 inhibitor and gamma emitting radioactive halogen (^{123}I) as imaging moiety.

Status of Claims

Claims 1 and 3-31 are pending, of which claims 5-9, 11, 15, 19-25 are withdrawn from consideration at this time as being drawn to non-elected species. Claims 1, 3, 4, 10, 12-14, 16-18 and 26-31 are readable upon the elected invention and are examined herein on the merits for patentability.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claim 31 is rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility. The claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e. results in a claim which is not a proper process under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd. V. Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 31 is also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Claims 1, 3, 4, 10, 14, 16-18 and 26-31 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The claims are drawn to an imaging agent comprising a synthetic caspase-3 inhibitor labeled with an imaging moiety, wherein the caspase-3 inhibitor has a k_i for caspase-3 of less than 2000 nM, and wherein following administration of said labeled caspase-3 inhibitor to the mammalian body in vivo, the imaging moiety can be detected either externally in a non-invasive manner or via use of detectors designed for use in vivo. While dependent claims such as claim 12 recite structural elements that identify the caspase-3 inhibitor having the claimed functional properties (a K_i for caspase-3 of less than 2000 nM), claim 1 is devoid of any structural elements that correlate to the function which is to be

achieved with the claimed composition. For example, a vast number of caspase-3 inhibitors may be found in the art including a large number small molecules, peptide sequences, etc. It is clear that Applicant was in possession of certain identified caspase-3 inhibitors including tetrapeptide of formula III, quinazoline, 2-oxindole sulphonamide, oxoazepinoidoline, compound of Formulas IV, V, pyrazinone, dipeptide of formula VI, or a salicylic acid sulphonamide of Formula XI, the specification as filed does not provide support that Applicant had possession of the invention as generically claimed by function alone in the instant claims. For example, to arrive at the claimed contrast agent, one would have to determine which small molecules or peptide sequences have the claimed inhibition properties to which out of an almost unlimited number of potential imaging moieties (radioactive, paramagnetic, optical, etc.) to be combined into a single agent, and further which out of an almost unlimited number of potential functional groups or chemical reactions would be necessary to derivatize and conjugate the moieties into a single agent having the claimed functional properties. Applicant's limited disclosure of a few particular compounds which have the claimed functional properties does not provide support that Applicant envisaged the invention as a whole which is broadly claimed solely by function. In the instant case, a definition by function alone does not appear to sufficiently describe the claimed invention because it is only an indication of what the agent does, rather than what it is. See MPEP 2163 and *EliLilly,* 119 F.3 at 1568, 43 USPQ2d at 1406.

Claim Rejections - 35 USC § 102

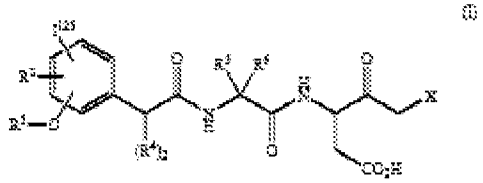
The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

The following references, drawn to non-elected species of inhibitor and/or imaging moiety were found during the search for the elected species. It should not be interpreted that a comprehensive search was performed for all non-elected species.

Claims 1, 3, 4, 14, 16-18, 26-28, 31 are rejected under 35 U.S.C. 102(e) as being anticipated by Colucci *et al.* (US 2006/0069038).

Coluccci discloses compounds of Formula I useful as caspase active site probes. These probes can be used to determine whether a caspase has been activated, in cells or in tissues of animal models of various pathologies (paragraph 0003).



See Figure 3, potency assessment caspase inhibitors by [^{125}I]-M808 labeling and by DEVD-AMC cleavage activity. Under the fluorogenic assay conditions K_i=$IC_{50/2}$ (paragraph 0006). Any suitable route of administration may be employed for providing a dosage of a compound of the present invention. For example, oral, parenteral and topical may be employed (paragraph 0228). Pharmaceutical carriers are disclosed (paragraph 0231-0232). See also synthetic methods in paragraph 0233 (e.g. $SnBu_3$).

Claims 1, 3, 4, 14, 16-18, 26, 28, 29 and 31 are rejected under 35 U.S.C. 102(b) as being anticipated by Haberkorn *et al.* (*Nuclear Medicine and Biology*, 2001, 28(7) p. 793-798), as evidenced by Deckwerth *et al.* (*Drug Dev. Research*), 2001, 52(4), p. 579-586).

Haberkorn discloses radioiodinated Z-Val-Ala-DL-Asp(0-methyl)-fluoromethyl ketone, [^{131}I]IZ-VAD-fmk, as a potential apoptosis imaging agent (abstract). A solution of [^{131}I]IZ-VAD-fmk in PBS containing 10% EtOH is disclosed (page 794, right column). ^{131}I is attached to Z-VAD-fmk through electrophilic substitution of the benzene ring (page 795).

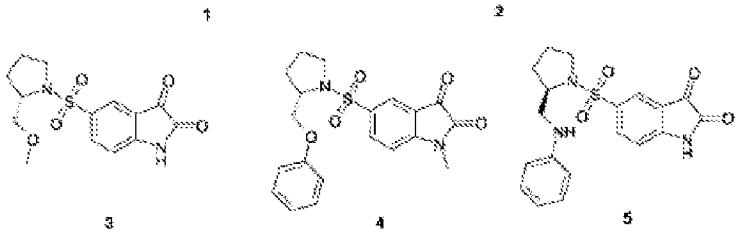
Normally, only one reference should be used in making a rejection under 35 U.S.C. 102. However, a 35 U.S.C. 102 rejection over multiple references has been held to be proper when the extra references are cited to: (A) Prove the primary reference contains an "enabled disclosure;" (B) Explain the meaning of a term used in the primary reference; or (C) Show that a characteristic not disclosed in the reference is inherent. For example, "to serve as an anticipation when the reference is silent about the

asserted inherent characteristic, such gap in the reference may be filled with recourse to extrinsic evidence. Such evidence must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill." *Continental Can Co. USA v. Monsanto Co.,* 948 F.2d 1264, 1268, 20 USPQ2d 1746, 1749 (Fed. Cir. 1991). See MPEP 2131.01.

In the instant case, the Deckwerth reference is included to show that K_i for zVADfmk is 820 nM.

Claims 26 and 28 are rejected under 35 U.S.C. 102(b) as being anticipated by Lee *et al.*, (*J. Biol. Chem.*, 2000, 275(21), p. 16007-16014).

Lee discloses potent and selective nonpeptide inhibitors of caspase 3 and 7 which inhibit apoptosis and maintain cell functionality (page 16007). See Figure 1. The compounds are isatin sulfonamide derivatives, such as compounds 3 and 4 having K_i = 60 and 15 nM, respectively. The claims require only that the precursor is "capable of" reaction with radioactive non-metal or halogen.



Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

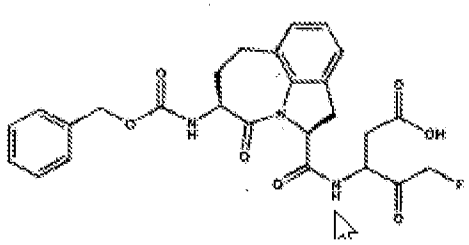
> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1, 3, 4, 12, 14, 16-18, 26-29 and 31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Deckwerth *et al.* (*Drug Dev. Research*), 2001, 52(4), p. 579-586) in view of Haberkorn *et al.* (*Nuclear Medicine and Biology*, 2001, 28(7) p. 793-798) and Colucci *et al.* (US 2006/0069038).

Deckwerth discloses that apoptotic cell death occurs in the injured and diseased central nervous system, and is mediated by a family of caspases, which are activated by lethal stimulus and cleave multiple protein substrates that are critical for cell viability. Novel small molecule peptidomimetic caspase inhibitor IDN5370/CCP82630, which belongs to the structural class of oxoazepinoindoline caspase inhibitors. It is 10-100 fold more potent than current peptidic inhibitors in inhibiting multiple caspases in vitro and promoting neuronal survival (see abstract).



Compared to zVADfmk, noncovalent binding of IDN5370 to caspase 1 and 3 as measured by its K_i is about 10 and 100 times tighter, with comparable or better first order rate constants of irreversible inactivation (page 581), see Table 1. The study suggests that peptidomimetic caspase inhibitors may penetrate the BBB and attenuate brain damage after peripheral, i.e., intravenous, administration (page 584).

Deckworth does not recite radiolabeled oxoazepinoindoline caspase-3 inhibitor.

Haberkorn discloses that caspases, once activated, play a key role in the intracellular signal cascade of cells undergoing apoptosis, and performed experiments to evaluate cysteine proteases of the caspase family as targets for the trapping of radiolabeled Z-VAD-fmk [benzyloxycarbonyl-Val-Ala-DL-Asp(O-methyl)-fluoromethyl ketone]. Z-VAD-fmk is an irreversible inhibitor of the cysteine protease intedeukin-l/3 converting enzyme (ICE) and was chosen, because it is successfully used as a pan-caspase inhibitor in apoptosis research. The study was undertaken to label Z-VAD-fmk with radioiodine at the phenyl moiety of the N-terminal Z-protection group and to assess the cellular uptake of IZ-VAD-fmk in apoptotic versus control cells (page 794). Radioiodinated Z-Val-Ala-DL-Asp(0-methyl)-fluoromethyl ketone, [^{131}I]IZ-VAD-fmk, as a potential apoptosis imaging agent (abstract). A solution of [^{131}I]IZ-VAD-fmk in PBS containing 10% EtOH is disclosed (page 794, right column). ^{131}I is attached to Z-VAD-

fmk through electrophilic substitution of the benzene ring (page 795). Activated caspases play a key role in the intracellular signal cascade of cells undergoing apoptosis. Therefore, these enzymes could serve as targets for the binding of radiolabeled substrates which in turn exhibit potential for the imaging of apoptotic cells. Z-VAD-fmk, an irreversibly binding pan-caspase inhibitor, was selected for labeling and biological testing in apoptotic cells assuming that caspase inhibitors selectively bind to activated caspases resulting in the trapping of their radiolabeled counterparts. This kind of trapping mechanism could be used for the non-invasive detection of apoptosis by the assessment of radiolabeled IZ-VAD-fmk accumulation. Furthermore, the measurement of activated caspases are thought to be more specific for the detection of apoptosis than the annexin V approach where also necrotic cells may contribute to the signal. An approach based on the visualization of caspase activation may detect early stages of apoptosis (797).

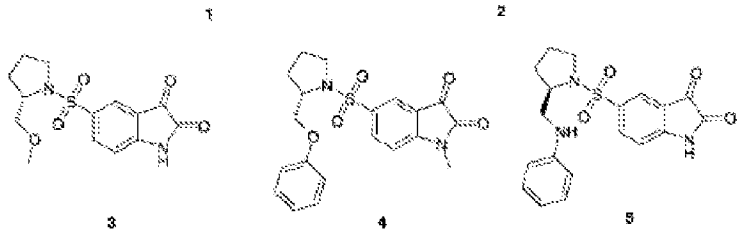
Colucci discloses compounds of Formula I useful as caspase active site probes. These probes can be used to determine whether a caspase has been activated, in cells or in tissues of animal models of various pathologies (paragraph 0003). See Figure 3, potency assessment caspase inhibitors by [^{125}I]-M808 labeling and by DEVD-AMC cleavage activity. Under the fluorogenic assay conditions K_i=$IC_{50/2}$ (paragraph 0006). Any suitable route of administration may be employed for providing a dosage of a compound of the present invention. For example, oral, parenteral and topical may be employed (paragraph 0228). Pharmaceutical carriers are disclosed (paragraph 0231-0232). See also synthetic methods in paragraph 0233 (e.g. $SnBu_3$ substitution).

It would have been obvious to one of ordinary skill in the art at the time of the invention to provide an iodine radiolabel on the oxoazepinoindoline caspase-3 inhibitor disclosed by Deckwerth. One would have been motivated to do so because Haberkorn discloses that ^{131}I radiolabeled caspase-3 inhibitor IZ-VAD-fmk may be useful in imaging of apoptosis. Colucci also discloses ^{125}I radiolabeled caspase-3 inhibitors as apoptosis probes. One would have had a reasonable expectation of success in doing so because Deckwerth teaches that compared to zVADfmk, noncovalent binding of IDN5370 to caspase 1 and 3 as measured by its K_i is about 10 and 100 times tighter, with comparable or better first order rate constants of irreversible inactivation. Furthermore, one of ordinary skill would have recognized that IDN5370 has structural features that would render it capable of similar radiolabeling procedures that were used in Haberkorn and/or Colucci (e.g. electrophilic substitution of the benzene ring). It would have been further obvious to provide the formulation in sterile form, since it is intended for intravenous administration, such as to minimize microbial infection, etc.

Claims 1, 3, 4, 12-14, 16-18, 26-29 and 31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lee *et al.*, (*J. Biol. Chem.*, 2000, 275(21), p. 16007-16014), in view of Haberkorn *et al.* (*Nuclear Medicine and Biology*, 2001, 28(7) p. 793-798) and Colucci *et al.* (US 2006/0069038).

Lee discloses potent and selective nonpeptide inhibitors of caspase 3 and 7 which inhibit apoptosis and maintain cell functionality (page 16007). See Figure 1. The compounds are isatin sulfonamide derivatives, such as compounds 3 and 4 having K_i =

60 and 15 nM, respectively. These inhibitors blocked apoptosis in murine bone marrow neutrophils and human chondrocytes. Furthermore, in camptothecin-induced chondrocyte apoptosis, cell functionality as measured by type II collagen promoter activity is maintained, an activity considered essential for cartilage homeostasis. These data suggest that inhibiting chondrocyte cell death with a caspase 3/7-selective inhibitor may provide a novel therapeutic approach for the prevention and treatment of osteoarthritis, or other disease states characterized by excessive apoptosis (abstract).



Lee does not specifically recite radiolabeled 2-oxindole sulphonamide caspase-3 inhibitors.

Haberkorn discloses that caspases, once activated, play a key role in the intra-cellular signal cascade of cells undergoing apoptosis, and performed experiments to evaluate cysteine proteases of the caspase family as targets for the trapping of radiola-beled Z-VAD-fmk [benzyloxycarbonyl-Val-Ala-DL-Asp(O-methyl)-fluoromethyl ketone]. Z-VAD-fmk is an irreversible inhibitor of the cysteine protease intedeukin-l/3 converting enzyme (ICE) and was chosen, because it is successfully used as a pan-caspase inhibitor in apoptosis research. The study was undertaken to label Z-VAD-fmk with radioiodine at the phenyl moiety of the N-terminal Z-protection group and to assess the

cellular uptake of IZ-VAD-fmk in apoptotic versus control cells (page 794). Radioiodinated Z-Val-Ala-DL-Asp(0-methyl)-fluoromethyl ketone, [^{131}I]IZ-VAD-fmk, as a potential apoptosis imaging agent (abstract). A solution of [^{131}I]IZ-VAD-fmk in PBS containing 10% EtOH is disclosed (page 794, right column). ^{131}I is attached to Z-VAD-fmk through electrophilic substitution of the benzene ring (page 795). Activated caspases play a key role in the intracellular signal cascade of cells undergoing apoptosis. Therefore, these enzymes could serve as targets for the binding of radiolabeled substrates which in turn exhibit potential for the imaging of apoptotic cells. Z-VAD-fmk, an irreversibly binding pan-caspase inhibitor, was selected for labeling and biological testing in apoptotic cells assuming that caspase inhibitors selectively bind to activated caspases resulting in the trapping of their radiolabeled counterparts. This kind of trapping mechanism could be used for the non-invasive detection of apoptosis by the assessment of radiolabeled IZ-VAD-fmk accumulation. Furthermore, the measurement of activated caspases are thought to be more specific for the detection of apoptosis than the annexin V approach where also necrotic cells may contribute to the signal. An approach based on the visualization of caspase activation may detect early stages of apoptosis (797).

Colucci discloses compounds of Formula I useful as caspase active site probes. These probes can be used to determine whether a caspase has been activated, in cells or in tissues of animal models of various pathologies (paragraph 0003). See Figure 3, potency assessment caspase inhibitors by [^{125}I]-M808 labeling and by DEVD-AMC cleavage activity. Under the fluorogenic assay conditions K_i=$IC_{50/2}$ (paragraph 0006).

Any suitable route of administration may be employed for providing a dosage of a compound of the present invention. For example, oral, parenteral and topical may be employed (paragraph 0228). Pharmaceutical carriers are disclosed (paragraph 0231-0232). See also synthetic methods in paragraph 0233 (e.g. $SnBu_3$ substitution).

It would have been obvious to one of ordinary skill in the art at the time of the invention to provide an iodine radiolabel on the 2-oxindole sulphonamide3 caspase-3 inhibitors disclosed by Lee. One would have been motivated to do so because Haberkorn discloses that ^{131}I radiolabeled caspase-3 inhibitor IZ-VAD-fmk may be useful in imaging of apoptosis. Colucci also discloses ^{125}I radiolabeled caspase-3 inhibitors as apoptosis probes. One would have had a reasonable expectation of success in doing so because Lee teaches that his compounds are potent and selective non-peptide inhibitors of the effector caspases 3 and 7 and that the inhibition of apoptosis and maintenance of cell functionality with a caspase 3/7-selective inhibitor is demonstrated, suggesting that targeting these two caspases alone is sufficient for blocking apoptosis. Accordingly, one of ordinary skill would have had a reasonable expectation of success in using the selective caspase-3 inhibitors of Lee as apoptosis probes, as was shown by Haberkorn and Colucci for other known caspase-3 inhibitors. Furthermore, one of ordinary skill would have recognized that compounds 4 and 5 of Lee have structural features that would render them capable of similar radiolabeling procedures that were used in Haberkorn and/or Colucci (e.g. electrophilic substitution of the benzene ring). It would have been further obvious to provide the formulation in

sterile form, since it is intended for intravenous administration, such as to minimize microbial infection, etc.

Claims 1, 3, 4, 10, 12-14, 16-18, 26-29 and 31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lee *et al.*, (*J. Biol. Chem.*, 2000, 275(21), p. 16007-16014), in view of Haberkorn *et al.* (*Nuclear Medicine and Biology*, 2001, 28(7) p. 793-798) and Colucci *et al.* (US 2006/0069038), further in view of Flanagan (US 5,601,801).

The rejection over Lee in view of Haberkorn and Colucci is maintained as above.

It would have been further obvious to provide ^{123}I radiolabeling when the teachings of Lee, Haberkorn and Colucci are taken in view of Flanagan.

Flanagan discloses angiotensin convening enzyme (ACE) inhibitors can be labelled with Iodine-123, Iodine-125, Iodine-127 or Iodine-131, useful to image the kidneys and lungs for diagnosis and treatment of diseases such as essential hypertension, renal artery stenosis, or diabetes which are associated with a change in the amount of ACE present in the human body (abstract, claim 1). Radiolabelled derivatives of lisinopril are labeled with Iodine-123, Iodine-125, Iodine-127 or Iodine-131 on the 2, 3, or 4 position of the phenyl ring (column 2, lines 5+).

It would have been obvious to one of ordinary skill in the art at the time of the invention to substitute ^{123}I as a functionally equivalent gamma-emitting radionuclide for ^{131}I or ^{125}I in the radiolabeled caspase-3 inhibitors of Haberkorn or Colucci, respectively. The Supreme Court in KSR International Co. v. Teleflex Inc., 550 U.S. ___, 82 USPQ2d 1385, 1395-97 (2007) identified a number of rationales to support a conclusion

of obviousness which are consistent with the proper "functional approach" to the determination of obviousness as laid down in Graham. One such rationale includes the simple substitution of one known element for another to obtain predictable results. The key to supporting any rejection under 35 U.S.C. 103 is the clear articulation of the reason(s) why the claimed invention would have been obvious. See MPEP 2143. In the instant case, the substituted components (^{123}I, ^{131}I or ^{125}I) and their functions were known in the art at the time of the instant invention. One of ordinary skill in the art could have substituted one known gamma emitting radioactive iodine radionuclide for another, and the results of the substitution would have been predictable, that is SPECT imaging of apoptosis using a radiolabeled caspase-3 inhibitor.

Claims 1, 3, 4, 12-14, 16-18, 26-31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lee *et al.*, (*J. Biol. Chem.*, 2000, 275(21), p. 16007-16014), in view of Haberkorn *et al.* (*Nuclear Medicine and Biology*, 2001, 28(7) p. 793-798) and Colucci *et al.* (US 2006/0069038), further in view of Hunter (US 7,018,610).

The rejection over Lee in view of Haberkorn and Colucci is maintained as above.

It would have been further obvious to perform radiolabeling using compounds conjugated to solid support when the teachings of Lee, Haberkorn and Colucci are taken in view of Hunter.

Hunter discloses that molecules labeled with radioactive isotopes have been used as both imaging agents in medical diagnosis as well as therapeutic agents in the treatment of cancer. Both radiolabeled small molecules and radiolabeled peptides and

nucleotides have been used to diagnose tumors. One common method of labeling molecules with radioactive isotopes for medical use is a stannylation process. While this process yields isotopically pure products, toxic tin by-products remain and must be separated before the radiolabeled molecules can be used. Furthermore, the unstable nature of radiolabeled molecules and their precursors lead to a short shelf life. Hunter's invention is directed to compounds that may be used to prepare radiolabeled compounds in an effective manner. The invention is also directed in part to methods of reparing radiolabeled compounds. One aspect of the present invention relates to polymer precursor compounds represented by: Poly--L--R—Y (column 1-2). A further aspect contemplates a kit including subject compounds, and optionally instructions for their use. Uses for such kits include therapeutic and medical imaging applications. In one embodiment, a kit containing a radiolabeling system is provided, which comprises a polymer precursor compound and instructions for using said polymer precursor compound, wherein said polymer precursor compound comprises the polymer precursor compound shown in structure 1. In a further embodiment, the kit includes a filter or a filtration device. Certain compounds of the invention are precursors for the rapid and efficient radiolabeling of compounds. Since radiolabeled compounds may have a very short shelf life, a stable precursor may be needed for storage until use. Another aspect relates to methods of synthesizing isotopically pure radiolabeled compounds without unwanted impurities (column 3, lines 20+).

It would have been obvious to one of ordinary skill in the art at the time of the invention to perform radiolabeling using compounds conjugated to solid support, and

one would have been motivated to do so because Hunter teaches that such methods provide known advantages such as reduced toxicity byproducts, improved product purity, improved shelf-life of radiopharmaceuticals. Furthermore, Hunter's methods include solid-supported stannylation processes, and both Haberkorn and Colucci employ stannylation in their radiosynthesis.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1, 3, 4, 10, 12-14, 16-18 and 26-31 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over the claims of copending Application No. 11/818,360. Although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of

claims are drawn to imaging agents comprising labeled caspase-3 substrates and an imaging moiety, including structurally overlapping peptide sequences. Accordingly the claims are overlapping in scope and are obvious variants of one another.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Objections

Claim 1 is objected to because of the following informalities: the claim lacks punctuation at the end of the sentence. Appropriate correction is required.

Conclusion

No claims are allowed at this time.

The following references are made of record as being relevant to the instant invention: US 2006/0147378 and 2004/0242494.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Leah Schlientz whose telephone number is 571-272-9928. The examiner can normally be reached on Monday - Friday 8 AM - 5 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Hartley can be reached on 571-272-0616. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for

published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Michael G. Hartley/
Supervisory Patent Examiner, Art Unit 1618

LHS